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ACMG STATEMENT

Solid organ transplantation in methylmalonic acidemia and propionic acidemia: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG)

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Introduction

Methylmalonic acidemia (MMA; OMIM 251000, OMIM 251100, OMIM 251110, OMIM 277410, OMIM 277400) and propionic acidemia (PA; OMIM 606054) are inborn errors of metabolism of the propionate pathway characterized by accumulation of methylmalonic acid and propionic acid, respectively, leading to acute presentations related to metabolic acidosis and hyperammonemia, as well as chronic heterogenous complications.

Isolated MMA is caused by deficiency of the enzyme methylmalonyl-CoA mutase or defects in transport or metabolism of its cofactor, adenosyl-cobalamin. The disorder is

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genetically heterogenous and can be caused by biallelic pathogenic variants in 1 of the 5 genes, *MMUT*, *MMAA*, *MMAB*, *MCEE*, and *MMADHC*. MMA can be classified into subtypes based on responsiveness to cobalamin. In general, patients who are cobalamin responsive are thought to have less severe phenotypes, although there are reports of renal failure and subsequent need for renal transplant in this population.[1] MMA can also be classified according to the amount of residual enzyme activity, namely mut^0 subtype for complete enzyme deficiency or mut^- subtype for partial enzyme deficiency. In natural history and large cohort publications, clinical severity of the condition is gauged by age of first symptoms; frequency of metabolic crises; neurodevelopmental delay; progressive end organ involvement, including renal involvement, metabolic strokes, hearing loss, and eye involvement; and serum levels of methylmalonic acid.[2,3]

PA is caused by deficiency of the enzyme propionyl-CoA carboxylase due to biallelic pathogenic variants in either the *PCCA* or *PCCB* genes. Similar to MMA, clinical severity has been classified based on age of presentation, neurologic outcomes (with metabolic strokes), end-organ complications (ie, cardiac arrhythmias, cardiomyopathies, optic atrophy, hearing loss), and frequency of metabolic crises.[4,5]

With current therapy, survival has improved as evidenced by a study focusing on the mut^0 subtype demonstrating improved patient survival over successive decades (0% in 1970-1979, 50% in 1980-1989, 78.9% in 1990-1997).[3] However, despite the improved observed survival, medical management can be inadequate in preventing long-term mortality and morbidity in individuals with MMA and PA. The treatment of PA with liver transplantation (LT) and of MMA with LT or kidney transplantation (KT) or combined liver and kidney transplantation (LKT) in patients with severe metabolic phenotype and/or end organ failure has been available in some locations for almost 2 decades.[6] The aim of this points to consider statement is to (1) review current practice related to organ transplantation, (2) provide general guidance in decision-making and management of patients being considered for or with completed transplants, (3) help design a framework for shared decision-making, and (4) outline known deficits in knowledge. However, many questions about long-term outcomes, single organ vs combined organ transplantation, as well as post-transplant medical and dietary management remain. Given these goals, the following points to consider are targeted to the medical genetics community and other disciplines that manage these patients regarding indications for transplantation, expected post-transplant outcomes, surveillance of potential complications, and post-transplant disease progression, as well as peri- and post-transplant nutritional management.

Methods

A literature search of PubMed was done with the range of January 1960 through March 2021 using the following Boolean search terms: ("propionic acidemia" OR "propionic aciduria" OR "methylmalonic aciduria" OR "methylmalonic acidemia") AND ("transplant" OR "liver transplant" OR "renal transplant"). Review of the search results by at least 2 of the authors identified 94 publications as applicable and formed the literature basis for the generation of this document (see Supplemental Table 1 for a full list of references).

Points to consider include the following:

1. The most common indication for transplantation in individuals with MMA and PA is severe early-onset disease with frequent episodes of metabolic decompensation. The decision to transplant and type of transplant indicated should be made after a thorough pretransplant evaluation by a multidisciplinary team consisting of biochemical geneticists, pediatric neurologists, transplant nephrologists, transplant gastroenterologists, transplant surgeons, dietitians, and social workers.
2. Transplantation leads to improvement or resolution in episodes of metabolic crises and stabilization of other end-organ complications, such as cardiomyopathy and renal dysfunction. There have been rare reports of decompensation and metabolic strokes in relation to surgery or several years after the procedure. Some degree of liberalization of protein restriction appears to be tolerated after transplantation, but it remains unclear if a completely unrestricted diet should be recommended.
3. Energy demands and catabolism are increased during the transplant procedure and in the early post-transplant period. Therefore, administration of sufficient caloric support is essential to prevent metabolic decompensation and promote a successful recovery.
4. Complications can be seen in relation to the graft, surgery (acute or chronic rejection, vessel thrombosis, infection, bleeding), use of immunosuppressants (infection, cancer, posterior reversible encephalopathy syndrome, and post-transplant lymphoproliferative disorder), or related to the disease itself.
5. Patients who have undergone a transplant should be followed up closely and receive periodic surveillance (as detailed in the discussion) pertaining to graft survival and use of immunosuppressants as well as for metabolic status and end-organ complications of the disease.

Discussion

Transplant-related considerations

Pretransplant evaluation

Decision-making for transplantation in PA and MMA should be made after consultation with a multidisciplinary team, including biochemical geneticists, pediatric neurologists, transplant nephrologists, transplant gastroenterologists, metabolic dietitians, surgeons, and social workers, to help inform benefit-risk assessment, timing for evaluation, and organ type selection. Reviews of up-to-date literature with families particularly in relation to survival, metabolic crisis, neurodevelopmental outcomes, and risks of immunosuppressive medications in the short and long term are a crucial part of pretransplant evaluation. Literature from the Urea Cycle Disorders Consortium has identified myriad perspectives, including clinical, social, and local health care systems, that should be integrated in the decision-making process.[7] For some patients, limited access to a metabolic center increases the risk for delayed interventions and worse outcomes. Access to care can drive decision-making with long-term, post-transplant care in some cases being more consistent and available than lifelong metabolic care, especially across the transition from pediatric to adult care.

Indications and organ type selection

The severity of the phenotype in PA and MMA ranges from severe neonatal forms to apparently asymptomatic cases with no clinical signs of the disease. The European registry and network for Intoxication type Metabolic Diseases (E-IMD) identified 22% (33 out of 149) of patients with MMA and 18.8% (19 out of 101) of patients with PA as asymptomatic (ie, never having an identified metabolic decompensation), with the remainder being symptomatic (experienced at least 1 metabolic crisis).[5] Although newborn screening (NBS) can impact mortality, neonatal onset and severe forms of PA and MMA often present before return of screen results.[2] Because of this, NBS appears to have little impact on intellectual disability and other morbidities. The differences in complications seen between early and late onset (diagnosis <30 days or >30 days of life) as a measure of severity show that the most severe cases have worse symptoms, which implies that reducing or preventing metabolic crises may improve outcomes.[2,3]

LT and LKT (and to some extent, KT) appear to markedly reduce but not necessarily eliminate the risk for metabolic decompensation and are associated with excellent short- to intermediate-term patient and graft survival.[8-12] There are multiple reports describing patients with PA and cardiomyopathy (including those who had severe cardiomyopathy, requiring left ventricular assist devices and extra corporeal membrane oxygenation) with heart function stabilizing after LT.[12-16] Chronic kidney disease and renal failure are known complications of MMA and have increasingly been identified in individuals with PA.[17] In these cases, LKT and KT have been used successfully to improve renal function and eliminate the need for dialysis.[1,18-21] Genotype−phenotype correlations are limited, and there is currently insufficient data to determine whether a milder metabolic phenotype would benefit from early transplantation to prevent long-term complications (such as renal dysfunction or cardiomyopathy). *Mut*⁻, *MMAA*-related, and *MMAB*-related cases of MMA are generally less likely to have severe decompensations and thus might result in a different risk-benefit analysis for transplantation.

KT alone has been performed in older patients with MMA who have renal failure (especially those with *MMAA* and *MMAB* genotypes).[22] These patients have few or no metabolic decompensations; therefore, renal dysfunction was the major deciding factor for KT, which is a lower risk procedure than LKT.[1,18,20] In contrast, there have also been reports of adult patients with PA who underwent successful KT or heart transplantation for acute renal failure[23] or dilated cardiomyopathy,[24] respectively. However, there is currently insufficient data to establish long-term efficacy in these situations and long-term longitudinal data are required. Renal transplantation in this patient population appears to stabilize biochemistry, but graft survival may be less favorable when compared with transplants done for other causes of renal failure. However, despite more frequent surgical complications of the LKT procedure, recent data suggest that LKT should be considered in individuals with chronic renal failure given improved metabolic outcomes, as well as the ability to liberalize protein restriction to some degree.[25] Current data on KT vs LKT in patients with MMA are limited to short follow-up. Thus, long-term studies comparing outcomes in individuals who have had KT vs LKT will be important for determining the risk-benefit analysis in the subset of patients with MMA and primarily renal complications. LT alone for PA increases metabolic stability but can be associated with nephrotoxicity from immunosuppressive medications. LT alone for MMA is being performed at early ages, before the onset of renal dysfunction, with a goal of preventing metabolic decompensations. Evidence on whether this approach can prevent renal failure later in life is still being gathered. LKT is predominately done for individuals with MMA who have some renal dysfunction and significant frequency of metabolic crises, because the risk of the procedure is considered less than the mortality and morbidity resulting from severe and frequent decompensations.

Perioperative dietary and fluid management

Optimal perioperative and postoperative dietary and fluid management are especially crucial for individuals with MMA and PA who undergo organ transplantation. Proper nutritional support in the perioperative period plays an integral role in successful organ transplantation in all organ recipients. In addition, optimal nutrition before and during LT improves patient and graft survival, helps to protect from infections, and decreases the risk of vascular complications, bile leak, and intestinal perforation.[26]

Energy demand and catabolism are increased in solid organ recipients because of anesthesia and surgical stress during the transplant procedure. The nutritional goals in the perioperative period center around prevention of catabolism to avoid metabolic decompensation.[27] Sufficient delivery of calories is also essential to promote wound healing and avoid infections.[26] During the perioperative fasting period, an infusion of 10% dextrose is typically started at a rate of 1.5 times the normal maintenance rate (by weight to approximate a glucose infusion rate of 8 mg/kg/min) while monitoring blood glucose levels and acid-base balance.[27-30] Patients with indications of metabolic decompensation should not undergo surgery. Poor metabolic status during LT carries a high risk for mortality and severe postoperative metabolic complication.[27]

In the early post-transplant period, energy demand and catabolism remain increased because of surgical stress during transplantation.[26] During this period, caloric support of 120% of basal energy expenditure is recommended.[31] It is essential to supply sufficient calories and minimize catabolism to prevent metabolic decompensations, but it can be challenging in the setting of early liver dysfunction and risk of developing lactic acidosis.[32] Parenteral nutritional support in the early postsurgery period is required, with the goal to transition to enteral nutritional support as soon as possible.[26,31] Typically, total parenteral nutrition with 5% to 20% dextrose should be initiated shortly after the transplant, providing 0.5 gm protein/kg/day and can be gradually increased with the goal to transition to enteral feeding as early as possible.[28,32] To provide additional calories, additional lipid emulsion can be used as tolerated. Resuming enteral nutrition within 12 hours of transplant has been shown to reduce postoperative viral infections and produce better nitrogen retention.[33] In the first 2 post-transplant months (acute phase), there is an increased need for nutrients and protein to promote healing and deter infection.[34] However, there is a lack of specific nutrition guidance during the perioperative phase in individuals with MMA and PA. Moreover, the optimal specific target for protein intake remains unclear.

Given the use of steroids in the acute post-transplant period, hyperglycemia may be noted. If hyperglycemia is present, patients need insulin to control glucose levels in the postoperative period, which may also help to promote anabolism.[28] Certain patients, especially the subset with cardiac complications, may require fluid restriction and in such situations, a higher dextrose content in the fluids will be required to achieve caloric goals. Those requiring insulin and high glucose infusion should be monitored for increases of lactic acid because of a potential interference with Krebs-cycle entry and inhibition of pyruvate dehydrogenase by toxic metabolites.[35] In the setting of lactic acidosis (plasma lactate >5 mmol/L), the use of insulin should be reconsidered.

Outcomes following transplantation

Outcomes related to graft survival and related complications

Outcomes from the United Network for Organ Sharing demonstrate that from 2002 to 2012, liver graft survival was 92% at 30 days, 89% at 1 year, and 83% at 5 years in organic acidemias and urea cycle disorder (UCD) groups.[36] These numbers are similar to the number of children who received LT for biliary atresia (91%, 88%, and 83%) and better than those with cholestatic disorders (95%, 86%, and 75%). The literature pertaining to KT for patients with MMA demonstrates 100% survival at 1 year and 83% survival at 5 years (Table 1).[1,37,38]

Complications from transplantation include perioperative issues, such as bleeding, vessel thrombosis, postoperative infection, and acute and chronic rejection. Monitoring of organ specific markers (Table 2) and acid-base status is recommended to assess recovery from acute graft injury. It is important to note that more surgical complications are seen in patients who are transplanted at younger ages or have lower weights.[36] Graft survival rate was 78% for children younger than 2 years of age and 88% for children older than 2 years. Higher weight at transplant was protective, but the risk was not significantly different between those weighing ≥5 to 10 kg and those weighing ≥10 to 20 kg.[36] Risk for surgical complications must be weighed against the risk of metabolic decompensation and consequential morbidities. Among the 17 patients with MMA who received LKT, there was liver graft loss in 1 patient due to hepatic artery thrombosis and retransplant was required within 15 days, which was successful.[36] Also inherent to any transplantation surgery, there is the risk of organ rejection, both early and late, which can be life-threatening.[13] However, more recent immunosuppressive regimens have decreased the risk of rejection, and this is evident when comparing the rejection rates and subsequent mortality in each decade since 1990. Although acute rejection occurs in about 40% of patients, chronic rejection is rare in LT, and current 10-year outcomes denote 85% survival.[39]

Immunosuppressive medications can result in a unique set of risks including infection, posterior reversible encephalopathy syndrome (PRES), and nephrotoxicity.[13] These complications have been mostly associated with tacrolimus; however, studies exploring the risks and safety profile of alternate immunosuppressive medications, such as sirolimus and mycophenolate mofetil, are limited. Moreover, there is an increased risk for cancers (such as hepatoblastoma) and post-transplant lymphoproliferative disease (PTLD).[13,40] The use of viral monitoring and empiric antiviral prophylaxis has significantly reduced the risk of Epstein-Barr virus driven PTLD in the recent era.[41] The most comprehensive approach is to take into consideration both allograft and nonallograft complications to achieve an ideal outcome metric with optimal graft function and low toxicity from immunosuppression.[42] In a patient population such as PA and MMA, surgery and anesthesia present singular risks because they can trigger metabolic crisis. Risks for complications vary from center to center based on providers' experience with common perioperative challenges.[6,13] PRES is a known complication of calcineurin-inhibitors and has been reported in individuals with PA and MMA after transplant.[43,44] PRES can present similarly to a metabolic stroke and imaging findings are crucial to recognize the entity. This complication usually responds to decreasing doses of antirejection medications.

Table 1 Summary of literature describing outcomes in LT and KT for MMA and PA

Authors/Reference	PA cases	Patient survival	Transplant graft survival	Postoperative outcomes	Notes
Yorifuji et al[11]	$N = 3$	100%	100%	Improvement in protein intake from 0.7 g/kg/day to 1.7 g/kg/day, one episode of acidosis with EPS resolved with support	Living related transplant from heterozygous parents
Charbit-Henrion et al[13]	$N = 12$ (17 LTs)	42% patient survival at 1 y	60% at 5 y	No metabolic decompensation among survivors with significantly relaxed protein restriction	Study period 1991-2013 CM resolved in 3 patients with pretransplant CM 3 patients with normal cardiac function developed CM and died post-transplant
Critelli et al[32]	$N = 3$	100% patient survival	100% graft survival	>1.2 mg/kg/day post-transplant protein intake	Significantly lower serum glycine levels post-transplant
Yap et al[6]	$N = 204$ (193 LTs, 2 KTs)	Post-transplant survival 86%	9 retransplants		CM reversed in 50% of cases in collective series of 38 manuscripts
Zhou et al[12]	$N = 70$	95% patient survival	91% graft survival	Pooled estimates for rejection, HAT, viral infection = 20%, 8%, 14%, respectively, 66% with liberalization of protein intake	Pooled estimates model
Pillai et al[10]	$N = 8$	100% patient survival at 5 y	90.9% graft survival		No CM pre or post transplant

The papers included in this table are intended to be representational of the literature and not comprehensive. In addition, examples of both single studies and metanalyses are included.

CM, cardiomyopathy; *EPS*, extrapyramidal symptoms; *HAT*, hepatic artery thrombosis; *KT*, kidney transplant; *LT*, liver transplant; *MMA*, methylmalonic acidemia; *PA*, propionic acidemia.

Outcomes related to metabolic crisis and dietary restriction

Episodes of metabolic decompensation typically are significantly reduced or eliminated after transplantation except for a few reports that describe rare episodes of acidosis (most commonly in those with living related donors) and/or metabolic strokes after transplantation.[10,29,45-49] In most of these cases, the metabolic crises resolved and were attributed to be a complication of the surgery entirely.[45,46,49] However, these patients can occasionally present later with decompensations with mildly elevated ammonia and acidosis (without ketones).[10]

Some degree of liberalization of dietary protein restriction appears to be tolerated after LT.[6,10,11,29,30,32,49-52] However, it remains unclear whether a completely unrestricted diet is advisable, and some patients who are prescribed a liberalized diet independently continue to pursue a mild protein restriction or vegetarian diet, confounding conclusions regarding the safety of completely unrestricted diets.[29,48,49] Although there is insufficient data to determine whether diet might be a contributing factor, there are several examples of metabolic stroke in individuals on an unrestricted diet,[29,45,49] but there is also at least 1 report of metabolic stroke post-transplantation in an individual on a restricted diet.[48] Particularly in MMA, the degree of underlying renal disease in patients without KT may also contribute to decision-making regarding protein restriction in individuals after LT. Moreover, there is little guidance in the literature regarding the appropriate ratio of natural protein to medical foods after LT in either disorder. Thus, further studies investigating the impact of an unrestricted diet vs restricted diet post-transplantation are needed in this setting.

Despite some degree of protein restriction in many cases after LT, several reports indicate an improvement in height after transplantation.[10,50,53] However, in some cases, these improvements may not become apparent for at least 2 years after transplantation given the confounding effect of corticosteroids,[10,53] and the data from 1 study suggest that these gains in height may be more apparent in individuals transplanted before 1 year of age.[53] Moreover, regardless of the protein prescription, in some cases, enteral tube feedings have been deemed no longer necessary post-LT because oral intake may improve in some individuals.[29,50,54,55]

Neurologic outcomes: Strokes and developmental assessment

Most of the large cohort studies and case series exploring long and short-term neurologic outcomes after LT suggest that most patients have no new strokes or developmental

Table 2 Evaluations to consider pre- and post-organ transplantation

Pretransplant evaluation[a]		Post-transplant surveillance	
Laboratory[a]		Laboratory[a]	
Immune		Immune	
	CD4		CD4
	Immunoglobulin G		Immunoglobulin G
	Donor-specific antibodies		Donor-specific antibodies
	Lymphocyte subsets		Plexiummune
	Vaccine titers (native)		Lymphocyte subsets
			Vaccine titers (native)
Metabolic		Metabolic	
	Ammonia		Ammonia (once after transplant then as needed)
	Total/free carnitine		Total/free carnitine (every 3 mo for first year, then every 6-12 mo)
	Plasma methylmalonic acid		Plasma methylmalonic acid (every 6-12 mo)
			Acylcarnitine (every 3-6 mo)
			Plasma amino acids (every 3-6 mo)
			Lactate (every 3-6 mo)
		Nutrition	
			25-hydroxyvitamin D (annually)
			Fasting lipid panel (every 3 mo first year, then every 6-12 mo)
			Iron studies (every 3 mo first year, then every 6-12 mo)
			Prealbumin (every 3 mo first year, then every 6 mo)
			Micronutrients (every 3 mo first year, then every 6-12 mo)[b]
Other		Other	
	Thyroid tests (eg, TSH, free T4)		CBC with differential (every 3-6 mo)
	Iron studies		Thyroid tests (eg, TSH, free T4) (every 3 mo first year, then every 6-12 mo)
	Fasting lipid panel		Parathyroid level (every 3 mo first year, then every 6-12 mo)
	Parathyroid level		Cystatin C level (every 3 mo first year, then every 6-12 mo)
	Cystatin C level		Urine protein/creatinine ratio (every 3 mo first year, then every 6-12 mo)
	Urine protein/creatinine ratio		AST (every 3 mo first year, then every 6-12 mo)
	AST		ALT (every 3 mo first year, then every 6-12 mo)
	ALT		GGTP (every 3 mo first year, then every 6-12 mo)
	GGTP		Bilirubin (every 3 mo first year, then every 6-12 mo)
	Bilirubin		
Imaging		Imaging	
	Echocardiogram		Echocardiogram (at least annually)
	EKG		EKG (at least annually)
	CTA/CT (or MRI/MRA) abdomen and pelvis		Dual-energy x-ray absorptiometry scan (usually first at 5-10 y, then every 5-10 y according to local standard of care)
			Brain MRI (as needed)
Screening		Screening	
	Eye exam (ophthalmology)		Eye exam (ophthalmology) (annually)
	Hearing evaluation		Hearing evaluation (annually)
	Developmental evaluation (neuropsychology evaluation) (age appropriate)		Developmental evaluation (neuropsychology evaluation) (age appropriate)

CBC, complete blood count; *CT*, computed tomography; *CTA*, computed tomography angiography; *EKG*, electrocardiogram; *MRA*, magnetic resonance angiography; *MRI*, magnetic resonance imaging; *TSH*, thyroid-stimulating hormone.

[a]Home transplant team may differ according to their local practices.

[b]Depending on diet adequacy, growth trajectory, and clinical signs; micronutrients to consider include vitamins B_{12} and B_6, erythrocyte folate, zinc, selenium, and essential fatty acids.

regression post-transplant; however, neuroimaging findings in some patients who had repeat scans showed volume loss, gliosis, etc.[10,46] Data also suggest that seizures and tremors might be common in the perioperative period.[56] There are some reports of patients having strokes years after transplant with or without a clear trigger. For instance, 1 patient with MMA has been reported who received LT at 9 months and remained relatively stable until 5 years of age when she had a metabolic stroke in the basal ganglia in the setting of a febrile illness.[45] A child with PA has been reported who presented with a fatal metabolic stroke 11 years post-LT without any evidence of biochemical decompensation.[48]

The etiology of these exceptional cases with sudden decompensation remains unclear and further functional studies are required to fully understand the risks. A magnetic resonance spectroscopy study in patients with neonatal-onset PA showed a significant decrease in basal ganglia glutamate plus glutamine and an increase in lactate during encephalopathic episodes. However, metabolite data from 2 children who had received LT were not significantly different from the comparator group.[57] The literature suggests that methylmalonic acid levels are elevated in the cerebrospinal fluid even after transplant, and it can lead to ongoing injury to the basal ganglia, which are areas in the central nervous system with high energy requirements.[46,56]

Studies evaluating long-term neurodevelopmental outcomes in patients with MMA or PA after transplantation are limited. Existing literature suggests that most patients maintained neurodevelopmental abilities or even made slight gains in motor and cognitive skills; however, a subset continued to be at risk for mild developmental delay, attention deficit hyperactivity disorder, and autism spectrum disorder.[10,18,25,29,58-61] One study compared the IQ and adaptative behavior in patients with UCD, maple syrup urine disease, and organic acidemias who received LT. Of these patients, 6 (46%) had intellectual disability, 5 (39%) had autism spectrum disorder, and 1 out of 13 (8%) had cerebral palsy, compared with 1 out of 26 (4%), 0, 0, and 0% of matched patients with LT but not inborn errors of metabolism, respectively. The neurocognitive and functional outcomes remained poor even after LT in patients with metabolic disorders, particularly in the UCD group.[62] Outcomes of MMA and PA cases from Taiwan showed that the IQ of the patients was improved after LT from 50 to 60.1 ($P = .07$) and the anxiety level of the caregiver was significantly reduced.[55] Another large study including 77 patients with MMA and 37 with PA reported that most patients who were tested had no change in their IQ after transplantation (76/94, 81%).[9] Therefore, counseling regarding developmental outcomes is crucial before transplantation to set appropriate parental expectations.

Outcomes related to end-organ complications

There are multiple reports of cardiomyopathy stabilizing or improving after orthotopic LT in patients with MMA or PA.[10,13-16,63] Although many reports suggest resolution of cardiomyopathy after LT,[13] other reports suggest that cardiomyopathy can recur or develop after transplantation.[64] There have also been documented cases of prolonged QTc interval in patients with PA after LT, which implies that this disease-specific complication is not necessarily eliminated by transplant.[62] Also, LT is contraindicated in some patients because of severe heart disease. Regarding renal complications, reports indicate that kidney function and neurologic status improve after LKT, but some patients have exhibited worsening renal function after LT.[51,65,66] Sakamoto et al[53] reported a patient who had pre-existing renal dysfunction before LT and developed renal failure from contrast used for endoscopic retrograde cholangiopancreatography. In addition, immunosuppressive medications may exert a toxic effect on the kidneys. It is important to consider that most patients with MMA have low muscle mass and therefore the serum creatinine and calculated estimated glomerular filtration rate cannot accurately reflect true renal function. However, a study showed that cystatin C and serum methylmalonic acid concentrations were highly correlated with smaller kidneys and decreased renal function.[67] Data regarding optic complications post-transplantation are also limited. There is 1 report of a patient who developed acute exacerbation of chronic bilateral optic neuropathy shortly after LT; however, it subsequently improved and remained stable.[56]

Surveillance after transplantation

Surveillance related to graft and immunosuppressive medications

All patients who receive LT, LKT, and KT are expected to require some level of immunosuppressive medications for their lifetime. As discussed previously, immunosuppression increases risks for infections, PTLD, and other cancers.[6,13,40,68] Routine post-transplant screening should include at least annual liver function tests (eg, AST, ALT, alkaline phosphatase, GGTP, bilirubin, and prealbumin), immunologic panel (donor-specific HLA antigens, Immunoplex, lymphocyte subsets, and IgG), kidney function tests (cystatin and urine protein and cells), parathyroid hormone level, and thyroid function tests (thyroid-stimulating hormone and free T4). The comprehensive metabolic panel should be monitored monthly for the first year and then every 3 months. In addition, neurocognitive assessment and neuroimaging (brain magnetic resonance imaging and magnetic resonance spectroscopy) should be obtained. Finally, the remainder of the interval testing is determined by center practice, which typically measures biochemical lab and immunosuppression medication levels every 2 to 3 months and may include protocol biopsies (Table 2).

Surveillance related to disease specific complications

There is an improvement in biochemical markers of the disease (propionylcarnitine, methylmalonic acid, and 2-methylcitrate) after LT, LKT, or KT, but these do not completely normalize.[32,37,52,56,69-72] When decompensation occurs post-transplantation, there is usually no signs of hyperammonemia, acidosis, or ketones and episodes are rather restricted to neurologic sequalae. Metabolic or neurologic decompensations are typically seen in patients with living-related, partial, or auxiliary grafts.[6,11,53,59,73,74] At first, third, and sixth month after transplantation and every 6 months thereafter, the following biochemical tests can be considered: plasma amino acids, lactate, plasma methylmalonic acid levels, acylcarnitine profile, and total/free carnitine levels. Also, to screen for progression of other long-term disease sequelae, patients should receive an annual echocardiogram, hearing screen, and eye examination consistent with current clinical recommendations.[64,75]

Surveillance related to nutritional status

Follow-up with a dietitian or nutritionist is critical for all patients after LT regardless of the reason for transplantation.[26] Thus, nutritional assessment is an important component of the post-transplantation monitoring in individuals with MMA and PA even in patients who pursue minimal or no protein restriction or in whom tube feeds are deemed no longer necessary. Immunosuppressive medications used after LT can impact various micronutrients (eg, potassium, magnesium, calcium, and phosphorus). Likewise, regardless of the indication for LT, bone health can be impacted after transplantation as a result of corticosteroid use, deconditioning, and other factors. Vitamin D deficiency is highly prevalent in pediatric patients post-transplantation; therefore, vitamin D levels should also be monitored. Although there are no specific recommendations for bone density scans, these can be considered in high-risk individuals.[26] Finally, given the prevalence of obesity and obesity-related disorders in individuals after LT, monitoring of body weight, body-mass index, and blood pressure has been recommended at each follow-up visit with annual evaluations of blood parameters to assess for hypertriglyceridemia, hypercholesterolemia, and insulin resistance.[26,76]

Conclusion and Future Directions

The use of LT in patients with PA and KT or LKT in patients with MMA who exhibit a severe metabolic phenotype and/or end-organ dysfunction has been established as a practice over the past 2 decades. Although there is some movement toward the implementation of organ transplantation for most patients with PA or MMA after diagnosis, a comprehensive risk-benefit analysis should be applied as an integral part of the decision-making process. An existing clinical challenge is the prediction of disease severity in neonates identified through NBS to determine which individuals would possibly most benefit from earlier transplantation to reduce episodes of metabolic decompensation associated with increased morbidity and mortality. In addition, existing questions that require future study include whether isolated LT in patients with MMA delay progression of renal dysfunction ultimately requiring KT. Also, does the timing of LT impact the incidence of cardiomyopathy post-transplant? Another question to answer is whether there is a level of pre-existing neurologic dysfunction for which transplantation will not provide tangible benefits? Importantly, systematic longitudinal studies, including neurodevelopmental assessments, functional neuroimaging, and other end-organ functional assessments in patients with PA or MMA post-transplant, are currently lacking. Further implementation of multicenter longitudinal studies in these populations are essential to provide valuable data to address outstanding questions.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

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Affiliations

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Supplemental Table 1. Literature Search Result Summary		
Authors	**PMID**	**Brief summary**
Alexopoulos, et al. 2020	31978012	27 PA liver transplanted, no difference for transplant for other indication for graft survival or survival, more post-op admissions
Ameloot, et al. 2011	21324476	16 yo, PA, required LV-Assist to bridge heart, then Liver transplanted and removed, normal function post-op
Arrizza, et al. 2015	26358860	22yo PA liver transplant with severe Cardiac dysfunction, 10 year follow up now 33 years, normal cardiac function no decompensations
Baba, Kasahara, et al. 2016	27221384	14 patients MMA liver transplant, periop complications and anesthesia
Bacchetta, et al. 2015	26270957	Summary of combined liver-kidney (and discussion of MMA) but also other indications
Barshes, Vanatta, et al. 2006	17032422	single institution with summary of literature - 12 PA liver transplant, outcomes, expert opinion
Brassier, et al. 2013	23751327	4 MMA renal transplants, outcomes and complications, some post-labs
Celik, et al. 2019	31392117	1 domino PA liver (plus other IEMS)
Chakrapani A, et al. 2002	11865284	9 mon, liver transplant MMA, stroke 5 y 6 month
Charbit-Henrion, et al. 2015	25683683	12 patients, 17 liver transplants (1991-2013), high mortality, resolved cardiomyopathy, lots renal dysfunction before and after
Chen, Hwu, et al. 2010	19686300	4 case with liver transplant, 4 without for MMA, tracking MMA levels pre and post
Chu, Chien, et al. 2019	30940196	2 6MMA, 1 cblB, 4 PA, LT shortened admission length, decreased TF, maybe improved IQ/DQ
Clothier J C, et al. 2011	21416195	8 years MMAB, renal transplant
Coman D, et al. 2006	16247646	14y B12-reponsive cblA; renal transplant
Cosson M A, et al. 2008	18676166	MMA, renal transplant 4 years, hepatoblastoma at 11 years
Criterilli, McKiernan, et al. 2018	30080956	9 patients PA/MMA ltx, l-ktxp, less metabolic decompensation, levels of MMA and NH3, stabilization of renal and heart,
Curnock, et al. 2020	31715057	14 PA with liver transplant (1995-2015) single institution, pre-and post-protein, indicaition, outcomes of graft, mortality,
Darwish A, et al. 2011	21376697	Liver transplant, summary for IEMs, including PA.MMA---summary of lit
Davison JE, et al. 2011	21554693	8 PA, MRI; MRS, two with liver transplants and not different fcomparisons
Duclaux-Loras, Bacchetta, et al. 2016	27060059	Combinws 1992-2013 (18 patients, 1 MMA)
Etuwewe B, et al. 2009	19048296	4 y MMA esrd, used peritoneal to bridge to 20 mon Renal transplant
Giussani, et al. 2016	26607205	PRES reported in MMA (liver-kidney) and anothher 10 days following transplant, change in meds-resolved
Hirotsu, et al. 2018	32026114	22 mon liver transplant MMA---anesthesia
Ho D, et al. 2000	10736088	20 month MMA liver transplant
Hörster F, et al. 2007	17597648	83 with MMA, outcomes
Hsui JY, et al. 2003	14521026	11 month MMA, liver transplant
Huang HP, et al. 2005	16276436	2 mma WITH LIVER TRANSPLANT 8 MONTHS AND 11 MONTHS, no decompensations, all received donor with EBV, one with CMV, outcomes
Jain-Ghai, Joffe, et al. 2020	32154059	neuropsych IQ/DQ in IEM liver transplant
Jiang, Zhou, et al. 2021	33422927	Outcomes for MMA s/p liver or liver-kidney transplant
Jiang, Sun, et al. 2019	31673536	7 mma liver transplant, outcomes
Jiang, Sun. 2019	30949461	lit review MMA LT CKLT survival, complications
Kamei, Ito, et al. 2011	21974703	HD prior to liver transplant for MMA, 7 patients
Kaplan P, et al. 2006	16750411	10 year MMA 9 years out of liver transplant, has denovo MMA in brain
Kasahara M, et al. 2006	17096763	3 own cases for MMA liveing related, liver tranplant
Kasahara M, et al. 2012	22151065	3 PA patients, review of literature, outcomes
Kayler L K, et al. 2002	12234269	1 PA 2MMA 28 metabolic patients, Liver transplant outcomes, PA one of deaths
Khanna, et al. 2016	26219882	Domino LT from MMA 28 year old
Kim TW, Hall SR, 2003	12846721	14 year old PA, liver transplant - anesthesia perspective
Lam C, et al. 2011	21549625	45 year old A, renal transplant,
Leonard, Walter, McKiernan. 2001	11405351	expert opinion
Li, et al. 2015	25990417	cost-effectiveness
Lubrano R, et al. 2001	11685586	17 year old MMA renal transplant
Lubrano R, et al. 2007	17401587	10 year followup above now 27 years, some tubulointerstitial disease, CM stable
Maines, et al. 2020	32681732	Methylcitric acid and other biomarkers - PA and MMA
Manoli, et al. 2018	30518688	FGF21 in MMA patients, reduced after liver transplant
Manzoni D, et al. 2006	16857001	2 cases, MMA anesthesia

Meyburg, Hoffman. 2005	16286891	expert opinion for LT includes discussion of timing
Molema, Williams, et al. 2020	32071844	2 MMA LKT; PRES? in one so did a evaluation of the literature for outcomes neurotexicity
Molema, Martinelli, et al. 2021	32996606	EUop experience, 20 MMA, 37 PA, liver; kidney or liver kidney in 57 MMA, undefined 8 MMA): survival, neurologic issues, IQ
Morath, Hörster, Sauer. 2013	22814947	renal disease seen in mma; reviews transplant
Morioka D, et al. 2005b	16212637	3 pa, 2 mma living donor, survival, growth,
Morioka, et al. 2005a	16177636	2 mma 3 PA Living donors, heterozygous donors; okay
Morioka, Kasahara, et al. 2007	17908273	7 MMA, liver transplant, outcomes
Nagao, et al. 2013	23151386	7 months PA transplant, neuro outcomes
Nagarajan S, et al. 2005	15902554	2 MMA liver-kidney
Neidich A, Neidich E. 2013	26894811	MMA transplant and ethics
Niemi, Kim, et al. 2015	25771389	MMA 14 liver, 8 KLT follow up and timeing. Survival complications, laboratory
Noone, Riedl, et al. 2019	30973671	5 MMA, liver or combined, discussed renal dysfunction follow transplant
Nyhan WL, et al. 2002	12111189	24 yo mma liver transplant, with renal dysfunction and neurological complications
Ou P et al., 2001	11434026	3 with PA, who dilated CM, one transplanted which cured cardiac complication
Perito, Rhee, et al. 2014	24136671	UNOS summary for 2002-2012
Pillai, Stoup, et al. 2019	31757659	9 pa/mma LT, 2 mma LKT
Quintero, Molera, et al. 2018	30242960	6 PA LT
Quintero, Molera, et al. 2019	30472769	Reply to comments for 30242960
Rajakamur, et al. 2016	26962256	2 PA liver transplant anesthesia
Rammohan, et al. 2019	30375139	PA summary of complications
Rela M, et al. 2007	17697263	10 year follow up for auxiliary PA
Romano S, et al. 2010	19818452	2 PA CM reversed with LT
Ross LF, 2010	20006764	ethical issues
Ryu, et al. 2013	24101962	22 mo with PA, liver transplant, anesthesia issues and labs
Sakamoto, et al. 2016	27670840	13 MMA liver transplant,
Sato S, et al. 2009	19207227	2 yo PA, ECMO required for arrhythmias, and CM, liver transplant done
Saudubray, Touati, et al. 1999	10603102	2 PA LT
Schlenzig J S, et al. 1995	7494403	2 PA, liver transplant (suspect same cohort at Saudebray 1999)
Shanmugam, et al. 2019	30311140	5 PA auxillary liver,
Shneider B, et al. 2011	213484526	commentary
Siegel, et al. 2020	33003354	5 MMAs, liver transplant, nutritional management
Silva, et al. 2017	26881497	2 PA LT
Sivananthan S, Hadžić N,2020	33205569	13 mo PA 1st Liver transplant, 5 years and 11 years post strokes.
Sloan, Manoli, Venditti. 2015	25882873	Commentary on Niemi, 25771389
Spada, et al. 2015	26362094	Commentary on Niemi, 25771389
Spada, et al. 2015	26077484	2 MMA early liver transplant, outcomes
Stevenson T, et al. 2010	19671092	3MMA; liver-kidney
Sutton VR, et al. 2012	21963082	Recommendations
Tuchmann-Durand, et al. 2020	32071836	Case report of medication prescription error in PA LT patient
Van Calcar SC, et al. 1998	9819702	24 year old MMA, renal transplant
van't Hoff W G, et al. 1998	9627602	13 year old MMA liver-kidney
van't Hoff W, et al. 1999	10603103	4 MMA patients Liver kidney
Vara, Turner, et al. 2011	21618686	5 PA liver transplants and outcomes
Vernon, et al. 2014	24961826	28 yo MMA, LKT, pre and post biochem analyses
Yap, et al. 2020	32270363	Review/Summary of the literature
Yorifuji T, et al. 2000	11035841	2 yo PA, liver transplant
Yorifuji T, et al. 2004	15159651	3 PA liver transplant
Zhou, Jiang, 2020	33093405	Review/Summary of literature